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*7* 8. In the preparation of a gel formulation which involves wet ball milling a calcipotriol component and adding the wet milled calcipotriol component to a gel base, the improvement which comprises wet milling calcipotriol hydrate as said component and using this wet milled hydrate for addition to said gel base, said hydrate being characterized by its  
storage stability at 40°C, its ready wettability and wet ball milling characteristics.

#### REMARKS

Favorable reconsideration is requested.

The courteous and helpful interview granted applicants' attorney by the Examiners on May 12, 1997 is acknowledged with appreciation.

As discussed with the Examiners, claims 1, 7 and 8 have been amended to include the subject matter of canceled claim 6 which further defines the characteristics of the claimed calcipotriol hydrate. The claims, as amended, are thought to be allowable for the reasons discussed at the interview and set forth below. It is understood that the claims, as amended, will be favorably considered by the Examiners.

At the interview, the Examiners were requested to reconsider the rejection of claims 1-8 (now claims 1-5, 7 and 8) under 35 USC 103 as being unpatentable over Calverley et al. ('048) in view of Jolly et al. ('325) because the cited references do not disclose or suggest the applicants' calcipotriol monohydrate as defined in the claims. Moreover, a skilled person reading the cited references would not find the motivation or suggestion to do what is alleged in the Office Action to obtain applicants' claimed monohydrate.

As discussed at the interview, Calverley discloses a generic group of vitamin D analogues and the compound calcipotriol. Calverley also discloses pharmaceutical compositions in a number of formulations and topical treatment of dermatological disorders.

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Calverley, however, does not disclose a monohydrate of calcipotriol as claimed. Jolly et al. disclose a monohydrate of  $1\alpha,25$ -dihydroxy-cholecalciferol which is different from the claimed monohydrate of calcipotriol.

Calcipotriol disclosed by Calverley et al. is useful for the topical treatment of psoriasis. It is desirable to formulate the calcipotriol in crystal form. To do this, the calcipotriol is usually subjected to a wet ball milling process in order to reduce the crystal size before the final suspension formulation is prepared. However, it has been found difficult to do this with the previously known form of calcipotriol crystals. In particular, these crystals are not easily wetted and during the milling process they form a stable foam which results in difficulties in obtaining a suitable small and uniform particle size.

The applicants have surprisingly found that the problems previously encountered with calcipotriol can be avoided by their invention of the previously unknown crystalline calcipotriol hydrate. This hydrate has been found to be easily wetted, readily wet ball milled and surprisingly stable at  $40^{\circ}\text{C}$ . This stability is to be contrasted with the available anhydrous form of calcipotriol which shows considerable decomposition at  $40^{\circ}\text{C}$ , e.g., more than 30% degradation after 12 months' storage. This is to be compared with no degradation after 12 months' storage at  $40^{\circ}\text{C}$  for the applicants' crystalline hydrate.

The Examiner concludes at page 3 of the Action that one having ordinary skill in the art would know from Jolly et al. that the hydrated form of  $1\alpha,25$ -dihydroxycholecalciferol is more stable than the anhydrous form of the same compound. Applicants respectfully disagree with this conclusion.

The reference merely states that the hydrated form is very stable but is silent about the stability of any other form of the compound, including the anhydrous form, which is not mentioned by the reference. Moreover, only the amorphous form and a chloroform solvate are mentioned (column 1, lines 28, 54 and 55).

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Jolly et al. are also silent about the meaning of the term "very stable". Vitamin D compounds are known as being relatively unstable and usually have to be stored in a deep freeze where these compounds may be very stable. The reference is silent about the temperature at which the hydrated form is "very stable". One having ordinary skill in the art would therefore not know from the reference, for example, whether the hydrated form is stable at room temperature or not.

The present claims are directed to the hitherto unknown monohydrate of calcipotriol which exhibits a surprisingly high stability for a vitamin D compound. The disclosed monohydrate is very stable at 40°C (still being within the drug substance specifications after two years at that temperature).

In contrast, the crystalline anhydrous form of calcipotriol (known from Calverley et al., 4,866,048) is very unstable at 40°C (more than 30% degradation in 12 months), unstable at room temperature, and very stable in a deep freeze.

In view of the above, the applicants maintain the position that Jolly et al. do not teach a person skilled in the art that the Jolly hydrate is more stable than the anhydrous form, to say nothing of the applicants' different hydrate.

The applicants acknowledge that the Jolly et al. reference teaches the use of a hydrate in pharmaceutical compositions. However, one skilled in the art would not know from the reference that the applicants' monohydrate would have superior technical properties over the anhydrous form. In the ball milling process used to obtain suitable small and uniform particles for use in suspension formulations, the crystals of the anhydrous form were not easily wetted and development of a stable foam gave rise to further difficulties. These technical difficulties were successfully overcome by the use of the claimed monohydrate and the ball milling of calcipotriol in the hydrate form is today an important step in the production of calcipotriol cream.

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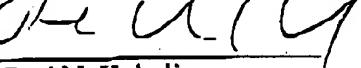
In summary, it is submitted that one could not deduce from the cited art that the applicants' crystalline monohydrate of calcipotriol would be more stable than the crystalline anhydrous form of calcipotriol disclosed by Calverley et al. Moreover, there is nothing in either of the cited references which suggests that the applicants' novel monohydrate would have the unique and unexpected properties discovered by the applicants. Accordingly, reconsideration and withdrawal of the Section 103 rejection are respectfully requested.

Reconsideration with allowance is requested.

Respectfully submitted,

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